REMARKS / ARGUMENTS

This amendment is in response to the Final Office Action mailed on 18 April 2007. Claims 24, 27, 29, 32 and 36 have been currently amended. Accordingly, claims 24, 26, 27-29, 32, and 35-37 are currently presented for examination. No new matter has been added by this amendment.

Objection for Claim numbering

The Examiner objects Claim 38 as not being numbered correctly. Applicant has renumbered Claim 38 to Claim 37 and the objection should now be fully addressed.

Rejection under 35 U.S.C. §112 (para. 1 and 2)

The Examiner alleges that Claim 29 and 36 reciting a method of treatment "in absence of protein degradation inhibitor" is vague and confusing. Applicant has amended Claim 29 and 36 to recite "in absence of protein breakdown inhibitor" (see support in PCT Publication, p.10 line 40-44). According to MPEP 2173.01, "Applicants are their own lexicographer" in the description. Applicant would like to submit that protein breakdown inhibitors indeed means commercially available drugs capable of decreasing proteinolysis and forcing protein degradation to reduce. Insulin, as seen in the instant specification, is one of the protein breakdown inhibitors. Tepic et al. (WO 03/063780, p.11 line 33 to p.12 line 3) has also stated that insulin is one of the protein breakdown inhibitors.

The Examiner also rejects Claim 32 as being indefinite and vague. Applicant has amended Claim 32 to recite "wherein said composition comprising isolated and purified recombinant human arginase I, said arginase having a specific activity of at least 336 I.U./mg, a purity of 80-100% and an extended half-life of at least 3 days" (see support in PCT Publication, Example 8C, 9A, 9B and 10). Claim 32 is now clear and withdrawal of rejection is respectfully requested.

Further, Claim 24, 26-29, 32 and 35-37 have been rejected as failing to comply with the written description requirement. Applicant has amended Claim 24 and 32 to recite a chemically modified, isolated and purified recombinant human arginase I having a specific activity of at least 336 I.U./mg, a purity of 80-100% and an extended half-life of at least 3 days.

Applicant would like to point out that, the lack of written description rejection must be made with "findings of fact which support the lack of written description conclusion. These findings should A) identify the claim limitation at issue and B) establish a *prima facie* case by providing reasons why a person skilled in the art at the time the application was filed would not have recognized that the inventor was in possession of the invention as claimed in view of the disclosure of the application as filed" (see MPEP 2164.04 I). Applicant would like to explain as follows:

A. Applicant respectfully point out that the claim limitation is a chemically modified, isolated and purified recombinant human arginase I having a specific activity of at least about 336I.U./mg, an extended half-life of at least 3 days and of 80-100% purity. Thus the arginase I in the aforesaid claims does not mean "***any*** modified arginase I". Not all kinds of modification would result in such a high specific activity, purity and extension of half-life, and those modifications that do not achieve the above-specified claim limitations would not be included into the scope of these claims.

B. According to MPEP 2163 I, "an applicant shows possession of the claimed invention by describing the claimed invention with all of its limitations...." Applicant submits that disclosure of the instant invention such as preparation of recombinant human arginase I (see Example 1 to 7), pegylation of the arginase I (see Example 8A to 8C), half-life determination of the arginase I (see Example 9A to 9B), and method of treatment using the modified arginase I (see Example 11 to 18) clearly shows possession of the "isolated and purified recombinant human arginase I" modified to have "a specific activity of at least 336 I.U./mg, a purity of 80-100% and an extended half-life of at least 3 days" as claimed. One skilled in the art would be able to reproduce the invention by following the aforesaid procedures. The present application has thus fulfilled the requirements of adequate written description (see MPEP 2163 II.3 (a)). Applicant therefore respectfully submits that examiner has failed to establish a prime facie case of lack of written description.

The Examiner also rejects Claims 24, 26-29, 32 and 35-37 on the ground that no enablement for a method of treatment of any malignancies is provided. According to MPEP 2163 II.3.a.ii, "the

written description requirement for a claimed genus may be satisfied through sufficient description of a representative number of species by actual reduction to practice." In the context of cancer, one skilled in the art would regards malignancies as a malignant tumor which can invade and destroy nearby tissue and may also spread. Malignancies may therefore be considered as a genus. Applicant respectfully submits that a representative number of species, i.e. different malignancies of different stages from different sites, have already been adequately described in the instant specification as summarized in Table 1 below. Thus the specification is sufficient to cover the claimed genus.

Lastly, the Examiner alleges that the specification does not support the pending claims by establishing detailed technical scheme and providing sufficient guideline (see the Final rejection, p.8 last para. and p.9 first para.). With reference to the inclusion of the specific examples in the specification, Applicant submits that the instant specification is sufficient to permit those skilled in the art to make and use the invention, wherein said invention is an isolated and purified recombinant human arginase I of at least 336 I.U./mg, 80-100% purity and an extended half-life for at least 3 days. According to MPEP 2164.01(b), "[a]s long as the specification discloses at least one method for making and using the claimed invention that bears a reasonable correlation to the entire scope of the claim, then the enablement requirement of 35 USC 112 is satisfied". Therefore, the Examiner's rejection is considered to be overcome.

In view of the aforesaid, Applicant respectfully requests 112 rejections on all pending claims to be withdrawn and request allowance for the pending claims.

Rejection under 35 U.S.C. §102 (e)

The Examiner rejects Claim 24, 26-29, 32 and 35-37 as anticipated by Tepic et al. Applicant has amended independent Claim 24 to recite an "isolated and purified recombinant human arginase I...., wherein said arginase comprising chemical modification resulting in a specific activity of at least 336 I.U./mg, a purity of 80-100% and an extended half-life for at least 3 days" (see support in Example 8C, 9A, 9B and 10). Applicant respectfully submit that "[a] claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in

a single prior art reference." *Verdegaal Bros. v. Union Oil Co. of California*" (see MPEP 2131). Applicant would like to point out that Tepic et al. discloses no chemically modified, isolated and highly purified recombinant human arginase I with specific activity of at least 336 I.U./mg and half-life for at least 3 days.

Moreover, MPEP 2121.02 II clearly states that "[w]hen a prior art reference merely discloses the structure of the claimed compound, evidence showing that attempts to prepare that compound were unsuccessful before the date of invention will be adequate to show inoperability." Applicant would like to point out that the Tepic reference has never been an enabling reference for producing isolated and highly purified recombinant human arginase I. Tepic mentions for example at page 7 line 19 to 20 that the arginase for use in the therapeutic methods disclosed therein may be pegylated and may be of human or recombinant form. However, whilst this disclosure is made in passing, there is no exemplification of how such a human recombinant form of a type I arginase may be produced, let alone an isolated and highly purified human arginase i.e. lack enablement. Tepic's disclosure is therefore inoperable.

According to page 21 of Tepic, the arginase Tepic used was in fact obtained from Prof. Ikemoto of the University of Kyoto. However, no further details such as purity and activity are provided as to how this pegylated arginase can be produced which would be necessary if this disclosure were to deprive the instant claims of novelty. It is noteworthy that the processes described by the University of Kyoto (and published in Ikemoto, Biochem J. (1990) 270, 697-703 before the priority date of the present application) for producing a recombinant human arginase do not lead to an arginase which is of comparable purity to the isolated and substantially purified arginase claimed in the instant amended claim set. In fact, the arginase produced according to the prior art methods (in particular by methods described in the aforesaid Ikemoto reference, which is referred to Example 10 of the present application) was estimated to be only 77% pure with approximately 23% contaminating protein. Table 2 is also attached to distinguish claim elements of the instant application from the Ikemoto arginase, as well as Tepic's disclosure.

One may argue that since the plasmid of Ikemoto is already described and constructed, it

would have been obvious for one skilled in the art to improve on the purification process in order to increase the expression and thereby increase the yield and purity of the protein of interest. However, Applicant would like to point out that biotechnology is an unpredictable art, and Applicant has recently discovered that the DNA sequence used by Ikemoto for cloning is for some unknown reason poorly expressed in the E. coli expression system that Ikemoto used. What Ikemoto constructed was a plasmid for containing the full-length human arginase I cDNA together with a 390 bases non-expressed downstream sequence found in the GenBank. Applicant, however, has discovered that the Ikemoto plasmid is very poorly expressed in E. coli, and in fact, E. coli transformed by the Ikemoto plasmid is unstable and the plasmid would be lost from the bacterial cell after 6 months of storage. The transformed Ikemoto E. coli cells would also easily die off. A high purity arginase I with low contaminating proteins thus cannot be achieved because the quantity of arginase 1 simply cannot be obtained using the Ikemoto system.

Serendipitously, the high purity and specific activity of the present invention was achieved in a B. subtilis expression system (see PCT pub., Example 1 to 7). The Ikemoto reference therefore is inoperable and non-enabling for the currently pending claims.

MPEP 2121.01 clearly states that "[t]he disclosure in an assertedly anticipating reference must provide an enabling disclosure of the desired subject matter; mere naming or description of the subject matter is insufficient, if it cannot be produced without undue experimentation." Tepic does not teach how to produce an isolated and purified recombinant human arginase I, of purity 80-100%, with specific activity and half-life comparable to the instant invention. Accordingly, Tepic is not considered to be citable against the claims of the present in so far as it purports to cover the subject matter directed to a human recombinant arginase in isolated and purified form.

Conclusion

In light of the amendments and arguments offered, Applicant respectfully requests removal of the 102 rejection. Allowance of the claims is respectfully requested.

Respectfully submitted,
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APPENDIX

Table 1

Example	Common types	Origin	Stage described in spec.	Reference (PCT)
Liver	Hepatocellular carcinoma	Hepatocytes	Dysplasia, carcinoma in situ	p.29, line 5 and line 11
Rectal	Adenocarcinoma, lymphoma and squamous cell carcinoma	Glandular tissue, epithelial cells	Metastasized	p.27, line 32
Breast	Ductal carcinoma, lobular carcinoma, inflammatory carcinoma and etc.	Glandular breast tissue	Dysplasia, carcinoma in situ	p.30, line 20 and line 26

Table 2

Claim elements	Instant Application	Tepic	Ikemoto
Isolated and highly purified recombinant human arginase I	Claim 24 and 32	This disclosure only discloses partially purified type I human liver arginase	This disclosure only discloses partially purified type I human liver arginase
Chemical modification resulting in an extended half-life for at least 3 days	Claim 24 and 28	Non-enabling description because no teaching on how to make the modified enzyme was provided	Non-enabling description because no teaching on how to make the modified enzyme was provided
Pharmaceutical composition reduces the physiological arginine level to below 10μM for at least 3 days	Claim 28	Did not specify reducing physiological arginine level.	Did not specify reducing physiological arginine level.
In absence of protein breakdown inhibitor	Claim 29 and 36	Clearly stated a protein breakdown inhibitor is required (p.11, last para.)	--